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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/066,782	02/06/2002	Gary L. Griffiths	329549	5555

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EXAMINER	
FETTEROLF, BRANDON J	
ART UNIT	PAPER NUMBER
1642	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/066,782	GRIFFITHS ET AL.	
	Examiner	Art Unit	
	BRANDON J. FETTEROLF	1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *20 December 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-6,8-14,48 and 49* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☒ Claim(s) *5,6,8-10 and 13* is/are allowed.

6)☒ Claim(s) *1-4, 11-12, 14 and 48-49* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Response to the Amendment

The Amendment filed on 12/20/2007 in response to the previous Non-Final Office Action (6/27/2007) is acknowledged and has been entered.

Claims 1-6, 8-14 and 48-49 are currently pending and under consideration.

Rejections Withdrawn:

The rejection of Claim 7 under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention because the specification does not provide evidence that the claimed biological materials are (1) known and readily available to the public; (2) reproducible from the written description is withdrawn in view of Applicants amendments.

New Rejections upon further consideration:

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1-4 and 48 remain rejected and claim 49 is rejected under 35 U.S.C. 103(a) as being unpatentable over Hansen et al. (WO 91/08770, 1991, of record) in view of Barbet et al. (US 5,256,395, 1993, of record).

Hansen teaches a method for increasing the target-specific toxicity of a drug, comprising pretargeting an enzyme to a human target cell; and administering a cytotoxic drug or a prodrug form thereof known to act at the target site, wherein the enzyme is capable of forming the active therapeutic agent (page 4, line 13 to page 5, line 2 and page 46, lines 4-5). Specifically, the WO document teaches that the enzyme is pretargeted to a target cell using an antibody-enzyme conjugate

(page 5, lines 14-15). With regards to the enzyme, the WO document teaches that suitable enzymes include, but are not limited to, glucuronidase, beta-glucosidase, beta-lactamase, cellulose, dextranase, fructose, aminopeptidase and lysozyme (page 9, lines 22-31). With regards to the antibody, the WO document teaches that the antibodies include, but are not limited to, monoclonal antibodies, antibodies having dual or multiple antigen or epitope specifities or fragments thereof including $F(ab')_2$, $F(ab)_2$, Fab', Fab and hybrid fragments (page 6, lines 22-30 and page 7, lines 11-22). Moreover, the WO document teaches that bispecific antibodies can also be used as the antibody-enzyme conjugate, wherein the bispecific antibody contains at least one binding site specific to an antigen at the target site and at least one other binding site specific to the enzyme component of the antibody-enzyme conjugate, thereby obviating the need to covalently conjugate the enzyme to the antibody (page 8, lines 24-37). Regarding the drug, the WO document teaches that the one type of anti-tumor drug that can be converted to a substrate for glucurodinase is an anthracycline glycoside referred to as epirubicin (page 14, lines 25-35). In addition, Handen teaches that the clearance of the antibody-enzyme conjugate and/or the substrate-enzyme conjugate can be accelerate by using a second antibody complex which recognizes the conjugate and enhances the rate of uptake by macrophages (page 25, lines 20-33). Thus, while Hansen does not explicitly teach that the epirubicin is detoxified to form an intermediate of lower toxicity, whereby the detoxified intermediate is reconverted to its more toxic form by the pretargeted enzyme, the claimed limitation does not appear to result in a manipulative difference in the method steps when compared to the prior art disclosure because the specification teaches (page 9, 3rd full paragraph) that drugs such as epirubicin which are detoxified in the liver to glucuronides such as epirubicin are suitable candidates for the site specific enhancement methods of the present invention. See Bristol-Myers Squibb Company v. Ben Venue Laboratories 58 USPQ2d 1508 (CAFC 2001). In the instant case, the mechanism of action does not have a bearing on the patentability of the invention if the invention was already known or obvious. Mere recognition of latent properties in the prior art does not render nonobvious an otherwise known invention. In re Wiseman, 201 USPQ 658 (CCPA 1979). Granting a patent on the discovery of an unknown but inherent function would remove from the public that which is in the public domain by virtue of its inclusion in, or obviousness from, the prior art. In re Baxter Travenol Labs, 21 USPQ2d 1281 (Fed. Cir. 1991). See M.P.E.P. 2145.

Hansen does not explicitly teach that the bispecific antibody comprises an arm which targets a low molecular weight hapten that is conjugate to said enzyme or administering a low molecular weight hapten that is conjugated to said enzyme.

Barbet et al. teach immunogical reagents consisting of a) antibody or fragment conjugates having both anti-cell specificity and anti-hapten specificity; and b) a synthetic tracer containing at least two hapten attached to radioactive isotopes, paramagnetic ions, drugs or toxins, wherein the reagents are capable of binding to target cells in a specific way, and the tracer localizes preferentially on the membrane of antigen-bearing cells even in the presence of excess antibody conjugate (column 4, lines 22-47).

Thus, it would have been prima facie obvious at the time the invention was made to modify the bispecific antibody as taught by Hansen et al. to include a bispecific antibody as taught by Barbet et al., and further to modify the pretargeting method as taught by Hansen et al. to include administration of an hapten-enzyme conjugate in view of the teachings Barbet et al. One would have been motivated to do so because Barbet et al. teach that the hapten conjugates localizes preferentially on the membrane of antigen-bearing cells even in the presence of excess antibody conjugate. Thus, one would have a reasonable expectation of success that by modifying the bispecific antibody as taught by Hansen et al. to include a bispecific antibody as taught by Barbet et al., and further modifying the pretargeting method as taught by Hansen et al. to include administration of an hapten-enzyme conjugate in view of the teachings Barbet et al., one would achieve a method of improving pretargeting an enzyme to the membrane of an antigen-bearing cell..

In response to this rejection, Applicants assert that neither Hansen nor Barbet disclose the element "wherein one arm of the bispecific antibody is targeted against a target site antigen and a second arm is targeted against a low molecular weight hapten that is conjugated to said enzyme, and administering a low molecular weight hapten that is conjugated to said enzyme." For example, Applicants assert that Hansen discloses a bispecific antibody wherein one arm of the antibody is either directly conjugated to the enzyme being targeted or is specific against the enzyme being targeted. In contrast, Applicants contend that the instant claimed subject matter discloses a bispecific antibody that is specific against a small molecular weight hapten to which any enzyme can be linked. Moreover, Applicants assert that Barbet et al. discloses a bispecific antibody that is specific against a low molecular weight hapten, but the hapten in Barbet is conjugated not to the

targeting enzyme, but to a therapeutic agent such as a radioisotope, paramagnetic ion, drug or toxin. In contrast, Applicants assert that the instant claimed subject matter, the paten is conjugated to the enzyme and the therapeutic agent is administered separately. In contrast, Applicants contend that in the instant claimed subject matter, the hapten is conjugated to the enzyme and the therapeutic agent is administered separately, which has the advantage of localizing the enzyme at the target site, so that the conversion of the detoxified therapeutic agent into the toxic form occurs at the target site and results in an increased active drug concentration at the target site. Furthermore, Applicants assert that the Barbet et al. teachings cannot be used for the construction of a hapten-enzyme conjugate since the design requirements disclosed are for constructing hapten-therapeutic agent conjugates, which are not suitable for constructing hapten enzyme conjugates. Secondly, Applicants assert that neither Hansen, nor Barbet disclose the element of "administering a cytotoxic chemotherapeutic agent known to act at the target site, or a prodrug for thereof which is converted to the chemotherapeutic agent in situ, which chemotherapeutic agent is also detoxified to form an intermediate of lower toxicity using said mammal's ordinary metabolic processes, whereby the detoxified intermediate is converted to its more toxic form by the pretargeted enzyme and thus has enhanced cytotoxicity at the target site. In particular, Applicants assert that the Hansen method specifically requires preparation and administration of a glucoronide derivative of the drug (see Hansen at Page 13, line 19-page 14, line 35), whereas the claimed subject matter teaches administration of an unaltered, cytotoxic form of the drug, which then may be converted to a glucuronide by the body's internal detoxifying mechanism. Lastly, Applicants assert that neither Hansen, nor Barbet contain any suggestion or motivation to modify or combine their respective teachings, and based on their disclosure a skilled artisan would not have any reasonable expectation of success in reaching the claimed subject matter.

These arguments have been carefully considered, but are not found persuasive.

First, it appears that Applicants are responding to the teachings of the references individually. However, it must be remembered that the references are relied upon in combination and are not meant to be considered separately as in a vacuum. It is the combination of all of the cited and relied upon references, which make up the state of the art with regard to the claimed invention. The test for obviousness is not whether the features of a secondary reference may be bodily incorporated into the structure of the primary reference and it is not that the claimed

invention must be expressly suggested in any one or all of the references; but rather the test is what the combined teachings of the references would have suggested to those of ordinary skill in the art. In re Keller, 642 F.2d 413, 208 USPQ 871 (CCPA 1981). In the instant case, the Examiner recognizes Hansen et al. discloses bispecific antibodies which are useful for pre-targeting therapy, wherein the bispecific antibody contains at least one binding site specific to an antigen at the target site and at least one other binding site specific to the enzyme component of the antibody-enzyme conjugate, thereby obviating the need to covalently conjugate the enzyme to the antibody (page 8, lines 24-37). Similarly, Barbet teaches bispecific antibodies useful for targeting therapy, wherein the antibodies have both anti-cell specificity and anti-hapten specificity. Thus, the references represent analogous teachings of using bispecific antibodies for the therapeutic purposes. Moreover, Barbet et al. provides the motivation to conjugate a hapten to an enzyme since hapten conjugates localizes preferentially on the membrane of antigen-bearing cells even in the presence of excess antibody conjugate. As such, one would have a reasonable expectation of success that by modifying the bispecific antibody as taught by Hansen et al. to include a bispecific antibody as taught by Barbet et al., and further modifying the pretargeting method as taught by Hansen et al. to include administration of an hapten-enzyme conjugate in view of the teachings Barbet et al., one would achieve a method of improving pretargeting an enzyme to the membrane of an antigen-bearing cell. Hence, Applicants arguments pertaining to the references individually have not been addressed. Secondly, regarding Applicants assertions with respect epirubicin as taught by Hansen et al., the Examiner acknowledges and does not dispute Applicants assertions that Hansen teaches preparation and administration of a glucoronide derivative of the drug. However, the Examiner recognizes that the claims do not appear to only require the administration of an unaltered chemotherapeutic agent as asserted by Applicants, but instead encompasses pro-drug forms of chemotherapeutic agents. As such, the glucuronide form of the chemotherapeutic agent epirubicin meets the limitation of a prodrug. Lastly, regarding Applicants contention that there is no suggestion or motivation to combine the teachings. The examiner recognizes that references cannot be arbitrarily combined and that there must be some reason why one skilled in the art would be motivated to make the proposed combination of primary and secondary references In re Nomiya, 184 USPQ 607 (CPA 1975). However, there is no requirement that an "express, written motivation to combine must appear in prior art references before a finding of obviousness." See Ruiz v. A.B. Chance Co., 357 F.3d 1270,

1276, 69 USPQ2d 1686, 1690 (Fed. Cir. 2004). For example, motivation to combine prior art references may exist in the nature of the problem to be solved (Ruiz at 1276, 69 USPQ2d at 1690) or the knowledge of one of ordinary skill in the art (National Steel Car v. Canadian Pacific Railway Ltd., 357 F.3d 1319, 1338, 69 USPQ2d 1641, 1656 (Fed. Cir. 2004)). References are evaluated by what they suggest to one versed in the art, rather than by their specific disclosures. In re Bozek, 163 USPQ 545 (CCPA 1969). As noted above, the Examiner recognizes Hansen et al. discloses bispecific antibodies which are useful for pre-targeting therapy, wherein the bispecific antibody contains at least one binding site specific to an antigen at the target site and at least one other binding site specific to the enzyme component of the antibody-enzyme conjugate, thereby obviating the need to covalently conjugate the enzyme to the antibody (page 8, lines 24-37). Similarly, Barbet teaches bispecific antibodies useful for targeting therapy, wherein the antibodies have both anti-cell specificity and anti-hapten specificity. Thus, the references represent analogous teachings of using bispecific antibodies for the therapeutic purposes. Moreover, Barbet et al. provides the motivation to conjugate a hapten to an enzyme since hapten conjugates localizes preferentially on the membrane of antigen-bearing cells even in the presence of excess antibody conjugate. As such, one would have a reasonable expectation of success that by modifying the bispecific antibody as taught by Hansen et al. to include a bispecific antibody as taught by Barbet et al., and further modifying the pretargeting method as taught by Hansen et al. to include administration of an hapten-enzyme conjugate in view of the teachings Barbet et al., one would achieve a method of improving pretargeting an enzyme to the membrane of an antigen-bearing cell.

Claims 12 and 14 remain rejected under 35 U.S.C. 103(a) as being unpatentable over Hansen et al. (WO 91/08770, 1991) in view Barbet et al. (US 5,256,395, 1993) and in further view of Griffiths et al (WO 96/40245, 1996, of record).

Hansen in view of Barbet et al. teach, as applied to claims 1-4, 11 and 48-49 above, a method for increasing the target-specific toxicity of a drug, comprising (a) pretargeting an enzyme to a human target cell, wherein said pretargeting comprises (1) administering a bispecific antibody or fragment thereof, wherein one arm of the bispecific antibody is targeted against a target site antigen and a second arm is targeted against a low molecular weight hapten that is conjugated to said enzyme and (2) administering a low molecular weight hapten that is conjugated to said enzyme; (b)

administering a second antibody complex which recognizes the conjugate and enhances the rate of clearance and (3) administering a cytotoxic drug or a prodrug form thereof known to act at the target site, wherein the enzyme is capable of forming the active therapeutic agent

Hansen in view of Barbet et al. does not explicitly teach that the antibody used during the clearing step is an anti-idiotypic antibody, wherein the anti-idiotypic antibody is specific for the paratope of the monoclonal antibody conjugate to the enzyme.

Griffiths et al. teach an improvement in *in vivo* pretargeting methods, wherein the improvement involves the administration of a clearing agent that binds to the primary binding site of the primary targeting species, whereby substantially only non-localized primary targeting species are cleared and targeted primary targeting species are not removed from the target site (page 6, lines 7-35). For example, the WO document teaches that when the primary targeting species is an antibody, the clearing agent comprises an antibody which recognizes the antigen binding region (paratope) of the targeting antibody, i.e., the clearing agent comprises an anti-idiotypic second antibody (page 9, lines 1-12 and page 10, line 38 to page 11, line 6).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to combine the method taught by Hansen in view of Barbet et al. with an anti-idiotypic antibody in view of Griffiths et al teachings of an improved method of in vivo pretargeting. One would have been motivated to do so because of Griffiths et al. teach that anti-idiotypic antibodies allow for the selective removal of non-localized targeting species and not the removal of targeting species from the target site. Thus, one of ordinary skill in the art would have a reasonable expectation that by using an anti-idiotypic antibody in the clearance step taught by Hansen in view of Barbet, one would achieve a method of improving pretargeting an enzyme-antibody conjugate for therapeutic purposes.

In response to this rejection, Applicants assert that since Griffiths does not teach the above discussed elements of claim 1, for the reasons set forth above Applicants submit that the rejection of these claims also be withdrawn.

These argument have been carefully considered, but are not found persuasive for the reasons set forth above and incorporated herein.

Claims 5-6, 8-10 and 13 appear to be free of the prior art; and therefore, appear to be in condition for allowance.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to BRANDON J. FETTEROLF whose telephone number is (571)272-2919. The examiner can normally be reached on Monday through Friday from 7:30 to 4:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Larry Helms can be reached on 571-272-0832. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Brandon J Fetterolf, PhD
Primary Examiner
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